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| 10/560,830 | 05/18/2006 | Marc Port | 3493-0155PUS1 | 8516 |
| 2292 7590 08/03/2010 BIRCH STEWART KOLASCH & BIRCH PO BOX 747 FALLS CHURCH, VA 22040-0747 | | | | |
| EXAMINER | | | | |
| SCHLIENTZ, LEAH H | | | | |
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

mailroom@bskb.com

Office Action Summary

Application No.

10/560,830

Applicant(s)

PORT ET AL.

Examiner

Leah Schlientz

Art Unit

1618

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 27 May 2010.
2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-44 and 46-60 is/are pending in the application.
4a) Of the above claim(s) 5,9-11,18,19,27-41,49,51-53 and 56-59 is/are withdrawn from consideration.
5) ☐ Claim(s) _____ is/are allowed.
6) ☒ Claim(s) 1-4,6-8,12-17,20-26,42-44,46-48,50,54,55 and 60 is/are rejected.
7) ☐ Claim(s) _____ is/are objected to.
8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☒ All b) ☐ Some * c) ☐ None of:
1. ☒ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-940)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date 12/15/2005, 8/23/2006, 9/29/2006, 5/27/2010
4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date _____
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____

DETAILED ACTION

Election/Restrictions

Applicant's election with traverse of Example 17 from pages 128-129 of the specification, including variables B, L, HR Ch (x, GNH, R, Q1, Q2, X, D, q, x, y, z) in the reply filed on 5/27/2010 is acknowledged. The traversal is on the ground(s) that there is not an undue search burden placed on the Examiner to examine the full scope of the present claims such that the Election Requirement should be withdrawn. Applicant notes that a significant majority of the pending claims recite compounds which share several significant core structural features, such that search and examination issues likely overlap with regard to these various compounds. This is not found persuasive because an examination and search burden may be established due to: inventions requiring a different field of search (e.g., searching different classes/subclasses or electronic resources, or employing different search queries); and/or the prior art applicable to one species would not likely be applicable to another species. In the instant case, the claims require at least employing different search queries of the varying distinct structural features of the instant claims. For example, the independent claims broadly include limitations such as "biovector," "linker," "polyfunctional molecule" (D), and various chelates, which amount to an extremely large number of potential compounds and would require multiple and differing search strategies be employed while performing a structure search. The argument that the various compounds share several significant core structural features is not found to be persuasive since in the

independent claims no actual structural features are provided for certain variables (e.g. linker, polyfunctional molecule), rather only the function of the various structural elements, therefore there are not necessarily overlapping core structural features. The requirement is still deemed proper and is therefore made FINAL.

Status of Claims

Claims 1-44 and 46-60 are pending, of which claims 5, 9-11, 18, 19, 27-41, 49, 51-53 and 56-59 are withdrawn from consideration as being drawn to non-elected species. Claims 1-4, 6-8, 12-17, 20-26, 42-44, 46-48, 50, 54, 55 and 60 are readable upon the elected species and are examined herein on the merits for patentability.

It is noted that the elected species compound is free of the prior art. In accordance with Markush practice, the search was expanded to include additional non-elected species in the independent claim.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-4, 6-8, 12-17, 20-26, 42-44, 46-48, 50, 54, 55 and 60 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claims are drawn to compound of general formula (E), including the limitation on line 9 of the fifth page of claim 1 such that "x, y and z are between 1 and 8, preferably x=1 to

3, $y=1$ to 6, $z=1-3$, given that $y=z$. A broad range or limitation together with a narrow range or limitation that falls within the broad range or limitation (in the same claim) is considered indefinite, since the resulting claim does not clearly set forth the metes and bounds of the patent protection desired. See MPEP § 2173.05(c). Note the explanation given by the Board of Patent Appeals and Interferences in *Ex parte Wu*, 10 USPQ2d 2031, 2033 (Bd. Pat. App. & Inter. 1989), as to where broad language is followed by "such as" and then narrow language. The Board stated that this can render a claim indefinite by raising a question or doubt as to whether the feature introduced by such language is (a) merely exemplary of the remainder of the claim, and therefore not required, or (b) a required feature of the claims. Note also, for example, the decisions of *Ex parte Steigewald*, 131 USPQ 74 (Bd. App. 1961); *Ex parte Hall*, 83 USPQ 38 (Bd. App. 1948); and *Ex parte Hasche*, 86 USPQ 481 (Bd. App. 1949). In the present instance, claim 1 recites the broad recitation that x, y and z are between 1-8, and the claim also recites various preferences for values of x, y and z, which is a narrower statement of the range/limitation.

Claims 4 and 12-15 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claim is drawn to a compound according to claim 1 wherein HR Ch represents structure II 1 in which $-S_1-T-S_2$ includes all three of B_1 , B_2 and B_3 representing $(CH_2)_xCONHR$ with $x = 1, 2, 3, \dots$ etc, line 8 of the claim. Variable $(CH_2)_xCONHR$ is repeated at lines 15 and 20. However, there does not appear

to be a description for variable R in the claim. It is noted that claim 1 from which claim 4 depends includes instances of R_1 , R' , R_a - R_i , R_2 , R_3 , however, there does not appear to be a variable R recited. As such, the metes and bounds of the claims are not clearly set forth and the scope of the invention cannot be distinctly ascertained. The claims have not been further treated on the merits because the identity of variable R is not set forth.

Claim 26 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claim is directed to a compound according to claim 20, wherein (E) is as shown in the figure of the claim. The figure includes variables AAG_1AA_{28} . However, the independent claims from which claim 26 depends do not appear to include a description for variables AAG_1AA_{28} . As such, the metes and bounds of the claims are not clearly set forth and the scope of the invention cannot be distinctly ascertained. The claim has not been further treated on the merits because the identities of variables AAG_1AA_{28} are not set forth.

Claim 42 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claim is directed to a compound according to claim 1, in its form bonded to an element M, (E) being written $B_x-L-(HR\ Ch)_y-M$; given that M is a paramagnetic metal ion having atomic number 21-29, etc". However, claim 1 shows chelate $I_{a,b,c,d,e,f,g}$ being bound to gadolinium in line 11 of claim 1. Accordingly, claim 42

is confusing because it fails to further limit the claim from which it depends but rather introduces additional metal ions that may be bound to the chelate.

Claim 50 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claim is drawn to a compound according to claim 6, wherein D is of 1,3,5-triazine type, of formula: linker 2, with linker 2 chosen from a) and b) and preferably a): c) etc... However, no description is provided for variables a) or b). As such, the metes and bounds of the claims are not clearly set forth and the scope of the invention cannot be distinctly ascertained.

Claim 60 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claim is rejected as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The claim is drawn to a method of diagnostic of a cardiovascular, cancer-related or inflammatory pathology comprising administration of a magnetic resonance contrast product according to claim 43 to a patient in need thereof. However, the only step in the claimed method is administration. However, in order to achieve a method of diagnosis, additional steps would be required such as imaging.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-4, 6-8, 12-17, 20-26, 42-44, 46-48, 50, 54, 55 and 60 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over the claims of copending Application No. 10/560,830 in view of Keana (US 5,567,411). The instant claims are drawn to a compounds of general formula E, $B_x-L_z-(HR\ Ch)_y$, in which B is a biovector, L is a linker, and HR Ch represents $[(D)_q - (I_{a,b,c,d,e,f})_j]$. The claims of the '875 Application are drawn to a compound of general formula E, $W-(A)_m$, in which W is a central nucleus and A represents $[(D)_q - (I_{a,b,c,d,e,f})_j]$. While the '875 application does not specifically recite a biovector on the central nucleus, it is well known in the art to include a biovector on a contrast agent, including a dendritic amplifier molecule having multiple terminal active groups (e.g. DOTA, DTPA) stemming from a benzyl core group, as shown by Keana (US 5,567,411; see abstract and structures), and doing so provides known benefits such as targeted imaging. Accordingly, the claims are overlapping in scope and are obvious variants of one another. This is a provisional obviousness-type double patenting rejection.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

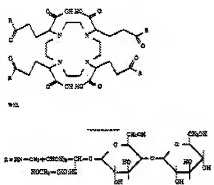
(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section

351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1, 7, 42-44 and 46-48 are rejected under 35 U.S.C. 102(b) as being anticipated by Meyer *et al.* (US 5,712,389).

Meyer discloses the compound in Example 7, including



Such compound reads on the instant claims such that B is a sugar (e.g. see R pictured above), L is a bond, HR Ch includes $q = 0$, $r = 1$, I_a includes X as COOH, R1 is a hydrophilic group of molecular weight greater than 200 selected from "polyol" or "polyhydroxyalkyl" (e.g. see R pictured above), U is $\text{CHR}_4\text{CON-linker 1}$, and R_4 is alkyl. It is noted that the instant specification defines at published paragraph 0007 that biovector may be a sugar.

With regard to claim 7, it is noted that L could also be interpreted as "alkoxyalkylene" depending on which portion of R pictured above is considered to be "B" in the instant claims.

With regard to claim 42, Gd, Mn, etc. are disclosed (column 2, line 15).

With regard to claims 43 and 44, contrast agent compositions for medical imaging by nucleic magnetic resonance including vehicles and additives are disclosed.

With regard to claim 46, it is noted that the intended use of the product is not given patentable weight to distinguish over Meyer because the intended use of the claimed invention must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. If the prior art structure is capable of performing the intended use, then it meets the claim. See *In re Casey*, 152 USPQ 235 (CCPA 1967) and *In re Otto*, 136 USPQ 458, 459 (CCPA 1963).

Claims 1, 2, 16, 17, 42-44, 46-48 and 60 are rejected under 35 U.S.C. 102(b) as being anticipated by Port *et al.* (*Mag. Res. Mat. In Phys. Biol. and Med.*, 2001, 12, p. 121-127).

Port discloses MRI contrast agent, P792, a gadolinium macrocyclic compound based on a Gd-DOTA structure substituted by hydrophilic arms. The chemical structure of P792 has been optimized in order to provide (1) a high relaxivity in the clinical field for MRI: 29 mM J x s⁻¹ at 60 MHz, (2) a high biocompatibility profile and (3) a high molecular volume: the apparent hydrodynamic volume of P792 is 125 times greater than that of Gd-DOTA. As a result of this high molecular volume, P792 presents an unusual pharmacokinetic profile, as it is a Rapid Clearance Blood Pool Agent (RCBPA) characterized by limited diffusion across the normal endothelium. The original pharmacokinetic properties of this RCBPA are expected to be well suited to MR coronary angiography, angiography, perfusion imaging (stress and rest), and

permeability imaging (detection of ischemia and tumor grading) (abstract). See structure of P792 shown in Figure 2.

Such a compound reads on the instant claims such that B is a an organic molecule (e.g. see R shown in Figure 2 of Port), L is a bond, HR Ch includes $q = 0$, $r = 1$, I_a includes X as COOH, R1 is a hydrophilic group of molecular weight greater than 200 selected option 1 in instant claim 2 (e.g. see R shown in Figure 2 of Port), U is CXR₄-linker 1, and R₄ is alkyl. It is noted that the instant specification defines at published paragraph 0007 that biovector may be an organic molecule. In this case, given the broadest reasonable interpretation of "biovector," biovector is interpreted to be an organic molecule (e.g. one of variable R shown in Port Figure 2), since the chelate itself is directed to blood vessels for anatomical vascular imaging; angiography coronary angiography (page 126).

With regard to claim 42, Gd, is disclosed (column 2, line 15).

With regard to claims 43 and 44, contrast agent compositions for intravenous injection are disclosed (page 124).

With regard to claim 46, it is noted that the intended use of the product is not given patentable weight to distinguish over Port because the intended use of the claimed invention must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. If the prior art structure is capable of performing the intended use, then it meets the claim. See *In re Casey*, 152 USPQ 235 (CCPA 1967) and *In re Otto*, 136 USPQ 458, 459 (CCPA 1963).

With regard to claim 60, coronary angiography is disclosed (page 126).

Claims 1-3, 6-8, 16, 17, 42-44, 46-48 and 60 are rejected under 35 U.S.C. 102(e) as being anticipated by Nachman *et al.* (WO 03/074523).

Nachman discloses macrocyclic high-relaxivity gadolinium chelate oligomers of formula $W(A)_m$ and their use as contrast product with vascular remanence for magnetic resonance imaging (abstract). Compounds include the Example 15 compound shown on page 61. See also compounds disclosed pages 7-29. See also claims.

Such a compound as Example 15 reads on the instant claims such that B is an organic molecule, L is a bond, D = triazine, $q = 1$, HR Ch includes $r = 2$, I_a includes X as COOH, R_1 is a hydrophilic group of molecular weight greater than 200 set forth in claim 2 of the instant claims, U is CXR₄-linker 1. It is noted that the instant specification defines at published paragraph 0007 that biovector may be an organic molecule. In this case, given the broadest reasonable interpretation of "biovector," biovector is interpreted to be an organic molecule, since the chelate itself is directed to blood vessels for anatomical vascular imaging (see page 2 discussing selective distribution in the vascular compartment).

With regard to claim 42, Gd, is disclosed.

With regard to claims 43 and 44, contrast agent compositions for intravenous injection are disclosed (page 1).

With regard to claim 46, it is noted that the intended use of the product is not given patentable weight to distinguish over Nachman because the intended use of the

claimed invention must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. If the prior art structure is capable of performing the intended use, then it meets the claim. See *In re Casey*, 152 USPQ 235 (CCPA 1967) and *In re Otto*, 136 USPQ 458, 459 (CCPA 1963).

With regard to claim 60, coronary angiography is disclosed (page 1).

Conclusion

No claims are allowed at this time.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Leah Schlientz whose telephone number is (571)272-9928. The examiner can normally be reached on Monday-Tuesday and Thursday-Friday 9 AM-5 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Hartley can be reached on 571-272-0616. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Michael G. Hartley/
Supervisory Patent Examiner, Art Unit 1618

LHS